SECTION 1 SCIENTIFIC ABSTRACT

Prostate cancer kills approximately 40,000 men annually. Although conventional therapies produce a high rate of cure for patients with early stage disease, a significant fraction of cancers recur and such therapies result in high morbidity. The prognosis for androgen-independent prostate cancer is much worse, for there is no effective treatment and a vast majority of these patients eventually succumb to the disease. There is a real need to develop new therapies that would reduce the morbidity associated with conventional therapies, decrease the incidence of tumor recurrence, and improve the outlook for recurrent and androgen-independent cancer.

Up to 80% of prostate cancer patients who receive external beam radiation therapy (EBRT) as their primary treatment will fail biochemically (develop a rising PSA) within 5 years. Unfortunately, limited therapeutic options exist for such patients. Further EBRT is not an option because of radiation-induced complications. Cytotoxic chemotherapy is not curative and is typically reserved for palliation with symptomatic progression or asymptomatic patients with significant biochemical progression following hormonal therapy. Of the four remaining therapeutic options, including salvage radical prostatectomy, salvage radiation therapy with interstitial implants, salvage cryoablation of the prostate, and androgen deprivation, none has demonstrated a high degree of efficacy in eradicating tumor with a reasonable degree of safety. Adjuvant therapies that increase the effectiveness of radiation therapy with low associated morbidity need to be developed.

The scientific rationale for this Phase I trial derives from research conducted in Drs. Kim's and Freytag's laboratories during the past seven years. Our research program has developed a novel, trimodal gene therapy approach for the treatment of prostate cancer. An E1 B-attenuated, replication-competent adenovirus (Ad5-CD/TK*rep*) is used to deliver a cytosine deaminase (CD)/herpes simplex virus thymidine kinase (HSV-1 TK) fusion gene to tumors. Preclinical studies have demonstrated that the Ad5-CD/TK*rep* virus itself generates a potent anti-tumor effect by replicating in, and preferentially destroying, human cancer cells. The therapeutic effect of the Ad5-CD/TK*rep* virus can be significantly enhanced by invoking two suicide gene systems (CD/5-FC and HSV-1 TK/GCV), which render malignant cells sensitive to specific pharmacological agents and sensitizes them to radiation. The safety of prongs 1 and 2 (Ad5-CD/TK*rep* viral and double suicide gene therapies) of our trimodal approach was recently evaluated in patients with local recurrence of prostate cancer after definitive radiation therapy (BB-IND 8436, RAC 9906-321). This Phase I trial is now completed. The treatment was well tolerated up to a vector dose of 10^{12} vp. Many of the toxicities observed were expected, minimal/mild (CTEP grade 1 or 2) and self-limiting.

The primary objective of the Phase I study described here is to evaluate the safety of using Ad5-CD/TK*rep* viral and double suicide gene therapies in a neoadjuvant setting with EBRT. The patient population will be men with locally advanced prostate cancer who will receive standard EBRT and are at high risk for failure (Stage T2a-T4; Gleason score ≥7; PSA ≥10 ng/ml but ≤30 ng/nl). The rationale for this trial is based on our

extensive preclinical work that demonstrated that both oncolytic viral therapy and double suicide gene therapy can be effective adjuvants to EBRT.